THE ENDOCRINE SOCIETY

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Division of Dockets Management (HFA-305)
Docket No. 2005N-0404
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

On behalf of The Endocrine Society, we appreciate the opportunity to submit comments in response to the October 7, 2005 *Federal Register* Solicitation of Public Review and Comment on Research Protocol: Gonadotropin-releasing Hormone Agonist Test in Disorders in Puberty [Docket No. 2005N-0404].

The Endocrine Society (Society) is a professional society comprising more than 11,000 physicians and representing the full range of professionals engaged in research and treatment of endocrine disorders such as diabetes, infertility, osteoporosis, thyroid disease, and obesity. In addition to researchers who focus on adult endocrine disorders, our membership also includes clinical investigators who conduct research on endocrine disorders affecting children and adolescents. We are therefore interested in the matters to be addressed by the FDA's Pediatric Ethics Subcommittee (Subcommittee) on November 15, 2005, in the context of the above-referenced protocol.

Background for Research Protocol: Gonadotropin-releasing Hormone Agonist Test in Disorders in Puberty

The protocol being considered by the Subcommittee has been sent by the University of Chicago Institutional Review Board (IRB) to OHRP for 407 review and is authored by Robert L. Rosenfield, M.D., a pediatric endocrinologist and Society member. It compares the sleep-related luteinizing hormone (LH) increase at puberty compared to the gonadotropin and sex steroid response to a gonadotropin releasing hormone agonist (leuprolide) test of pituitary-gonadal function. Sleep-related LH release is one of the earliest signs of puberty and is the gold standard for distinguishing those children for whom there is merely a delay in the timing of puberty from those with more serious causes. However, determination of sleep-related LH secretion requires intensive blood sampling and monitoring. The purpose of the study is to provide a means of assessing children with delayed puberty that is safe and less invasive than the current gold standard. At issue is the recruitment of healthy children as controls. Leuporolide is used in the routine diagnostic testing to assess the initiation of puberty. While this is a highly useful test that is considerably less invasive than the determination of sleep-related LH secretion, normative data are both sparse and a necessary prerequisite for the precise diagnosis of pubertal disorders in children.

The University of Chicago IRB approved the above protocol previously, and the study has been initiated. However, despite the absence of adverse events associated with the protocol, the IRB raised concerns that the potential risk associated with it may represent "minor increase over minimal risk" in healthy children and thus, under current federal regulations, must go to OHRP for review by a 407 panel The IRB classified the protocol in this category due to the length of hospitalization (more than 24 hours) and the use of leuprolide. These factors have been determined to represent more medical attention than a healthy child would "ordinarily encounter in daily life or during the performance of routine physical or psychological examinations or tests."

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Since the Society does not review clinical protocols and cannot issue statements regarding the risk-benefit ratio of a specific project, our comments will not address the details of the particular protocol referenced above. Instead, the Society's comments will focus on the use of healthy children as control subjects in clinical research.

Use of Healthy Children as Control Subjects in Clinical Research

The Society supports the participation of normal children as control subjects in clinical research under clearly defined circumstances. We maintain that the use of healthy children as control subjects is critical to the success of studies that focus on the treatment of children, and any regulation of the process must allow for the use of control groups to validate diagnostic and therapeutic interventions. Without carefully performed studies in normal children, research to advance the treatment of disease in children will suffer. Studies in normal children may in some circumstances be the only basis for determining safety and efficacy of medications and medical tests that are critical for the diagnosis and treatment of diseases in children. The Society would argue that the regulations stipulating 407 review may substantially constrain the enrollment of normal children as control subjects in clinical research.

Further, we strongly believe that although protection of children must be guaranteed, clinical protocols must be allowed to proceed through review in a timely and efficient manner. While one cannot argue that all benefit from careful review of clinical research on children, the increasingly narrow interpretation of acceptable risk is of particular concern. The Society does not support the concept that any pharmaceutical, even if approved for children and routinely used in diagnostic testing, should be considered a "minor increase over minimal risk," and hence, by its use in healthy children, mandates a review by a 407 panel. The Society calls for the rational use of the 407 review process, with a system in place to provide greater guidance to IRBs for determining "minor increase over minimal risk" that is based on scientific and ethical expertise and is consistent at a national level. Such a system would maintain careful consideration for the protection of children yet not inhibit the conduct of research that is critical for the diagnosis and treatment of diseases in children.

The Endocrine Society appreciates the opportunity to provide comments on this important issue. We urge the Subcommittee to consider these factors as it makes its decision for the specific protocol referenced above and for protocols that are referred for 407 review in the future.

Please do not hesitate to contact Janet Kreizman, Director of Government & Professional Affairs for The Endocrine Society at jkreizman@endo-society.org if we may provide any additional information or assistance as you move forward.

Sincerely,

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President
The Endocrine Society